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The higher dietary inflammation is associated with a higher burden of multimorbidity of cardio-metabolic and mental health disorders in an urbanizing community of southern India: A cross-sectional analysis for the APCAPS cohort

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ABSTRACT

Background & aims: Habitual dietary pattern has been shown to be a major modulator of systemic inflammation and is considered a modifiable risk factor for cardio-metabolic diseases (CMDs) and mental health disorders. We examined whether dietary-inflammation is associated with the multimorbidity of CMDs and mental health disorders in urbanizing-villages in southern India. We hypothesized that the participants with higher dietary-inflammation would have a higher burden of multimorbidity.
Materials & methods: We conducted a cross-sectional analysis of 5984 adults (53% male) participating in the Andhra Pradesh Children and Parents' Study. We assessed dietary-inflammation using dietary inflammatory index (DII®) based on intake of 27 micro- and macro-nutrients which were measured using a validated food-frequency-questionnaires. The CMDs and mental health disorders were assessed using standardized clinical procedures and validated questionnaires. 'Multimorbidity' was defined as a co-existence of one or more CMDs (hypertension, diabetes, myocardial infarction, heart failure, angina and stroke) and one or more mental health disorders (depression and anxiety). The association of multimorbidity with dietary-inflammation was examined using robust Poisson regression.
Results: The prevalence of multimorbidity was 3.5% and ~75% of participants were consuming a pro-inflammatory diet (DII >0.0). As compared to the 1st DII-quartile (least dietary-inflammatory group), the adjusted prevalence ratio (95% confidence interval) for the presence of multimorbidity was 1.46(0.87, 2.46) for 2nd, 1.75(1.05, 2.89) for 3rd, and 1.77(1.06, 2.96) for 4th DII-quartile (p-trend = 0.021). There was no evidence of an interaction between DII and sex on multimorbidity.
Conclusions: Dietary-inflammation had a positive linear association with the multimorbidity, which suggest that even modest reduction in dietary-inflammation may reduce the multimorbidity burden.

1. Introduction

The burden of cardio-metabolic diseases (CMDs, such as coronary heart disease, stroke, heart failure, hypertension, and diabetes) [1] and mental health conditions (such as depression, anxiety etc.) [2] is increasing in India owing to changes in demographics, lifestyles and environmental exposures. There is evidence of a bi-directional relationship between CMDs and mental health conditions and these conditions often cluster together in a given individual (commonly referred as 'multimorbidity') due to shared risk factors (lifestyle, biological, environmental, and genetic) and common underlying pathological mechanisms (for example chronic/systemic inflammation) [3]. Data suggest

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that patients with multimorbidity of CMDs and common mental health disorders have a higher rates of hospitalization, poor health outcomes, an increased risk of premature mortality, and reduced quality of life than those who have individual conditions [4]. This highlights the need to explore the common causes and mechanisms underlying this clustering to inform well-timed, high impact, and contextually relevant public health interventions to prevent or delay the onset of individual conditions as well as their clustering.

Existing evidence supports the role of chronic low-grade inflammation in the pathophysiology of CMDs and various mental health conditions (including anxiety and depression) [5–10]. Habitual dietary pattern, among others (dyslipidemia, infection, injury, smoking, air pollution etc.) have been shown to be a major modulator of the systemic inflammatory state and have potential as a preventive/therapeutic tool in diseases with inflammation as an underlying pathophysiologic mechanism [11,12]. Pro-inflammatory dietary patterns (diets rich in simple carbohydrates and saturated fat) have been shown to increase the risk of CMDs and mental health conditions [5–7]. Whereas anti-inflammatory dietary patterns (diet rich in fruits and green leafy vegetables (FGLV), whole grains, legumes and olive oil) reduce systemic inflammation and are thought to be cardio-protective [13].

Assessing dietary inflammation is challenging because diets are complex and dynamic over time and different foods are consumed together and not in isolation. Therefore, it is important to assess the overall inflammatory potential of a diet. The dietary inflammatory index (DII®) is a novel scoring algorithm developed based on a review of pre-clinical and clinical studies (n ~2000) examining the effect of different nutrients on six systemic inflammatory markers: C-reactive protein, interleukin (IL)-1β, IL-4, IL-6, IL-10, and tumour necrosis factor-α and standardized in reference to global composite diet database from 11 countries [14]. The DII quantitatively evaluates the overall inflammatory potential of a diet and ranks individual dietary pattern on a continuum from the maximal anti-inflammatory to the maximal pro-inflammatory potential [14].

To our knowledge, however, the few studies exploring the role of dietary inflammation on coexistence of CMDs and mental health conditions are limited to high income countries [15,16]. No work has been done to investigate the extent to which chronic low-grade inflammation may play a role in multimorbidity of CMDs and common mental health disorders in India. Hence, we examined the association of dietary inflammation with the multimorbidity of CMDs and common mental health disorders using data from the Andhra Pradesh Children and Parents Study (APCAPS) set in 29 rural and urbanizing villages in southern India [17]. We hypothesized that the participants with higher DII score would have a higher burden of multimorbidity (Fig-1).

2. Materials & Methods

2.1. Study population

We have used cross-sectional data from the third follow-up of the APCAPS cohort (2010-12), where standardized data on socio-demographic variables, CVD risk-factors, CVD morbidities and common mental health conditions was collected for 6944 participants residing in 29 villages surrounding Hyderabad, India [17]. The study was carried out in accordance with the principles of Helsinki Declaration. We obtained ethics approvals from the London School of Hygiene & Tropical Medicine (London, UK) [LSHTM Ethics Ref: 21771]; the ICMR-National Institute of Nutrition (Hyderabad, India) [NIN Protocol Number: 04/I/2020] and the Indian Institute of Public Health (Hyderabad, India) [IIPHH/TRCIEC/18 9/2018]. We also sought approval from the village heads and their committees in each of the study villages. Prior to their inclusion, all participants gave written informed consent or witnessed thumbprint if illiterate. For this study, we considered adults (age ≥18 years), with non-missing values for DII and multimorbidity. Our final sample size was 5984 (53% males).

2.2. Variable measurement

As published elsewhere [17,18], at clinics established within the villages, trained interviewers using standardized questionnaires conducted interviews to assess socio-demographic characteristics, health behaviours (smoking, alcohol intake, diet and physical activity), medical history (diagnosis and medication use for hypertension, diabetes, coronary heart disease, stroke, and depression) and household characteristics of study participants (questionnaires available at apcaps.lshtm.ac.uk). Participants underwent a physical examination (for body weight, height, blood pressure measurement) and a laboratory assessment for fasting blood biomarkers following standard operating procedures. Detailed processes to measure/calculate height, weight, body mass index (BMI), standard of living index (SLI), physical activity, blood pressure and fasting sugar have been described previously [17,18]. Physical Activity Level (PAL) was calculated using a formula: person's total energy expenditure over a 24-h period divided by his/her basal metabolic rate.

2.3. Dietary inflammation assessment

Diet was assessed by a purposively developed and validated (using multiple weighed 24-hr dietary recalls) 100-item semi-quantitative food frequency questionnaire (FFQ) [19]. The trained interviewer administered questionnaire, assessed average portion size and frequency of the selected local food items consumed over the past year. Portion size was assessed by showing examples of utensils (bowl, ladle, tablespoon,

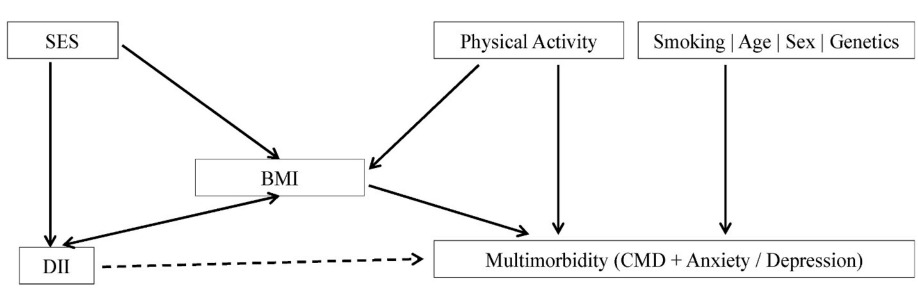

Fig. 1. A directed acyclic graph to showing the presumptive causal relationships between DII and Multimorbidity for the APCAPS cohort
APCAPS, the Andhra Pradesh Children and Parents Study; BMI, body mass index; SES, Socio-economic status; CMD, cardio-metabolic diseases; DII, dietary inflammatory index; Multimorbidity (defined as a co-existence of one or more CMDs (hypertension, diabetes, myocardial infarction, heart failure, angina and stroke) and one or more mental health disorders (depression and anxiety).
We tested the hypothesis: the participants with higher DII score would have a higher burden of multimorbidity of CMDs and common mental health disorders among participants from the APCAPS cohort set-up in 29 rural and urbanizing villages in southern India.

teaspoon, glass) to the participants, who were asked to report portion sizes in relation to these standards. Prior to the study, weighed recipes were collected from resident of the study area who were food preparers and combined with Indian food composition tables (or international sources if unavailable) to develop study-specific nutrient databases [19].

Following the published DII algorithm, we used 27 derived food parameters to assess inflammatory potential of diets [14]. These were alcohol, carotene, carbohydrates, cholesterol, total energy intake, fat, fibre, folate, iron, magnesium, monounsaturated fatty acids, omega-3 fatty acids, omega 6 fatty acids, pepper, polyunsaturated fatty acids, protein, saturated fat, selenium, vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin B12, vitamin C, vitamin E and zinc [14]. Information about remaining 18 food parameters: caffeine, eugenol, garlic, ginger, onion, saffron, turmeric, flanan-3-ol, flavones, flavonols, flavonones, green tea, anthocyanidins, isoflavones, thyme/oregano, transfat, rosemary, and vitamin D was unavailable. We calculated z-scores and centered percentile for each individual (for each food parameter) using standard global dietary means and standard deviations [14]. The centered percentile score (for each food parameter) was then multiplied by its corresponding 'overall food parameter-specific inflammatory effect score' to obtain the 'food parameter specific DII score' [14]. These scores were added to create a DII-score for each participant. The DII-score was validated in the study sample using C-reactive protein (a systemic inflammatory marker). There was a linear and positive association between the dietary inflammatory index and the CRP. The level of CRP was rising with the increase in the quartiles of DII-score (p-trend <0.001). The DII-score for the study ranged from −4.41 to +4.18. A higher DII-score (more than 0) reflects an elevated intake of pro-inflammatory nutrients, while a lower DII-score (less than 0) indicates elevated intake of anti-inflammatory nutrients in the diet.

2.4. Multimorbidity assessment

We defined multimorbidity as a co-existence of one or more CMDs (hypertension, diabetes, myocardial infarction, heart failure, angina and stroke) and one or more mental health disorders (depression and anxiety). Non-multimorbidity means participants may have one CMD or one mental health disorder or none. For this study, participants with a previous history of hypertension diagnosis by a clinician and/or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg were considered as hypertensives. Participants with a previous history of diabetes diagnosis and/or fasting glucose ≥126.0 mg/dL were considered as diabetics. Participant with prior clinical diagnosis of angina, myocardial infarction, heart failure, or stroke were considered to have CVD. Additionally, we used Rose questionnaire [20] to assess the angina status of participants. We used brief patient health questionnaires (PHQ) to assess the depression and anxiety [21]. Participants responding 'yes' to the question "In the last 4 weeks, have you had an anxiety attack – suddenly feeling fear or panic" were considered to have 'anxiety'. To assess depression, we asked participants to rate the depressive symptoms over last two weeks described in PHQ-9 [22]. Scores of 0, 1, 2, and 3, were assigned to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively. Participants with a-score ≥5 were considered to have depression [23].

2.5. Statistical analyses

We created the quartiles of DII with 1st quartile and 4th quartile reflecting participants with maximal anti-inflammatory and pro-inflammatory dietary pattern, respectively. Across different DII-quartiles as well as multimorbidity status (absent vs. present): (i) age, BMI and PAL were expressed as means and standard deviation (SD); (ii) SLI as medians and interquartile range (IQR); and (iii) categorical variables were expressed in percentages. P-values for trend across DII-quartiles status were determined using: linear regression when a response variable was continuous with a normal distribution; quartile regression when a response variable was continuous with skewed distribution; and logistic regression when a response variable was categorical. Across multimorbidity status: continuous variables with approximately normal distribution were compared using unpaired *t*-test; continuous variable with skewed distribution were compared using Mann-Whitney-U test; and categorical variables were compared using Pearson's chi-squared test. We also expressed the median (IQR) of 27 nutrients across DII-quartiles as well as Multimorbidity.

To evaluate the adjusted association of DII with multimorbidity, we used Poisson regression with a robust variance estimator to directly estimate prevalence ratios (PR) for cross-sectional data. We first calculated age- and sex-adjusted PR for DII-quartiles with multimorbidity as an outcome. We further adjusted for socio-demographic (occupation and education) and lifestyle variables (tobacco consumption, BMI, and PAL) to assess the independent association of DII with multimorbidity. We assigned medians to each quartile and treated it as a continuous variable to assess the linear trend across increasing DII-quartiles. Additionally, we conducted a propensity score analysis to account for the differences of various confounders between the levels of outcome variable (multimorbidity) and to reduce the risk of residual confounding. We repeated the analysis by using different definitions of multimorbidity. All p-values were two-tailed and a p-value <0.05 was considered as significant. Stata version 14.2 (Stata Corp, College Station, TX, USA) was used for all statistical analyses.

3. Results

Overall, the mean (SD) age of study participants was 36.2 years (13.8) with 3179 (53.1%) participants being males. The DII ranged from −4.41 to +4.18 with median (IQR) equal to 1.44 (0.07, 2.57). Participants with higher DII-quartiles (compared to lower DII-quartiles) were older, more likely to be women, smokers, less educated, and more physically active. Participants with higher DII-quartiles also had lower SLI, lower BMI, higher prevalence of CMDs, and mental health morbidities, and higher multimorbidity (Table-1).

There was a linear decrease in concentrations of all nutrients (anti-inflammatory as well as pro-inflammatory) except total cholesterol with increase in DII-quartiles (SI-table 1).

There was nearly consistent increase in the proportions of multimorbidity sub-components with increase in DII-quartiles. Participants with higher DII quartiles had higher prevalence of hypertension, diabetes, CHD, stroke, and depression. About 30.3% 35.6%, 44.5%, and 49.1% participants in the first, second, third and fourth DII-quartile, respectively, had either one or more sub-components of multimorbidity (Figure-2).

The age- and sex-adjusted prevalence (95% confidence interval) of multimorbidity among participants in the first, second, third and fourth DII-quartile was: 2.5% (1.5%, 3.5%), 3.2% (2.3%, 4.2%), 3.8% (2.9%, 4.7%), and 4.0% (3.1%, 5.0%), respectively. The increasing prevalence of multimorbidity (with increasing DII-quartiles) appeared to be mainly driven by the mental health disorders (SI-Fig. 1A, 1B, 1C).

Total number (%) of participants with defined multimorbidity were 210 (3.5%). Participants with multimorbidity were older (45.4% vs. 35.9%), more likely being females (52.9% vs. 46.7%), more current smoker (38.6% vs. 24.1%), less educated, and physically less active (74.3% vs. 69.4%). They had higher mean BMI (22.46 vs. 20.88) and higher median DII score (2.09 vs. 1.41) (Table-2).

Participants with multimorbidity or individual conditions (CMDs or mental health morbidities) had lower concentrations of all nutrients except total cholesterol and vitamin B12 (SI-table 2).

There was a positive trend for a higher prevalence of multimorbidity with higher DII (Figure-3). In an unadjusted model, compared to the first quartile, participants in the second, third, and fourth DII-quartile were likely to have 59%, 130% and 189% higher probability of multimorbidity, respectively. These probabilities were reduced to 46%, 75%, and 77% (for the second, third, and fourth DII-quartile), respectively,

Table 1
Distribution of socio-demographic, clinical and multimorbidity across DII-quartiles (n = 5984).

Socio-demographic and clinical parameters		DII Quartiles (n, DII range)				p-trend[a]
		Q1 (1496; −4.41, 0.06)	Q2 (1496; 0.07, 1.44)	Q3 (1496; 1.44, 2.57)	Q4 (1496; 2.57, 4.18)	
DII, median (IQR)		−0.89 (−1.65, −0.36)	0. 80 (0.45, 1.14)	2.07 (1.78, 2.34)	3.06 (2.81, 3.38)	–
Age in years, mean (SD)		30.5 (11.5)	34.0 (13.0)	38.6 (13.8)	41.8 (13.9)	<0.001
Male, n(%)		1061 (70.9)	833 (55.7)	752 (50.3)	533 (35.6)	<0.001
Standard of living score, mean (SD)		31.8 (8.2)	29.7 (8.2)	27.6 (8.0)	25.2 (8.0)	<0.001
Education, n(%)	No formal education	260 (17.4)	484 (32.3)	717 (47.9)	909 (60.8)	<0.001
	Primary	369 (24.7)	356 (23.8)	342 (22.9)	284 (19.0)	
	Secondary	691 (46.2)	511 (34.2)	341 (22.8)	241 (16.1)	
	Beyond secondary	176 (11.8)	145 (9.7)	96 (6.4)	62 (4.1)	
Occupation, n (%)	Unemployed	18 (1.2)	12 (0.8)	13 (0.9)	6 (0.4)	<0.001
	Housewife & retired & student	420 (28.1)	430 (28.7)	336 (22.5)	364 (24.3)	
	Unskilled laborer	431 (28.8)	594 (39.7)	795 (53.1)	880 (58.8)	
	Manual (semi-skilled & skilled)	488 (32.6)	363 (24.3)	280 (18.7)	210 (14.0)	
	Skilled non-manual & Semi-professional & professional	139 (9.3)	97 (6.5)	72 (4.8)	36 (2.4)	
Physical activity level, mean (SD)		1.59 (0.21)	1.61 (0.22)	1.64 (0.21)	1.63 (0.21)	<0.001
Moderate to vigorous physical activity (yes), n(%)		356 (23.8)	455 (30.4)	523 (35.0)	489 (32.7)	<0.001
BMI in kg/m^2, mean (SD)		21.4 (3.8)	21.1 (3.8)	20.9 (3.6)	20.4 (3.6)	<0.001
Current smoker (yes), n(%)		338 (22.6)	317 (21.2)	400 (26.7)	416 (27.8)	<0.001
CMDs (yes), n(%)		272 (18.2)	314 (21.0)	404 (27.0)	407 (27.2)	<0.001
Mental health disorders (yes), n(%)		140 (9.4)	167 (11.2)	193 (12.9)	248 (16.6)	<0.001
Multimorbidity (yes), n(%)		27 (1.8)	43 (2.9)	62 (4.1)	78 (5.2)	<0.001

APCAPS, the Andhra Pradesh Children and Parents Study; BMI, body mass index; CMDs, cardio-metabolic diseases; DII, dietary inflammatory index; IQR, inter-quartile range; n, frequency; %, percent; Q1, Q2, Q3, Q4 quartiles of DII; SD, standard deviation.
CMDs included hypertension, diabetes, MI, heart failure, angina, and stroke; mental health disorders included depression and anxiety; 'Multimorbidity' was defined as a co-existence of one or more CMDs and one or more mental health disorders.
Participants were classified as current smokers if they reported current use of cigarettes or having stopped smoking within the past 6 months.
[a] p-trend shows a p-value for linear trend across DII-quartiles.

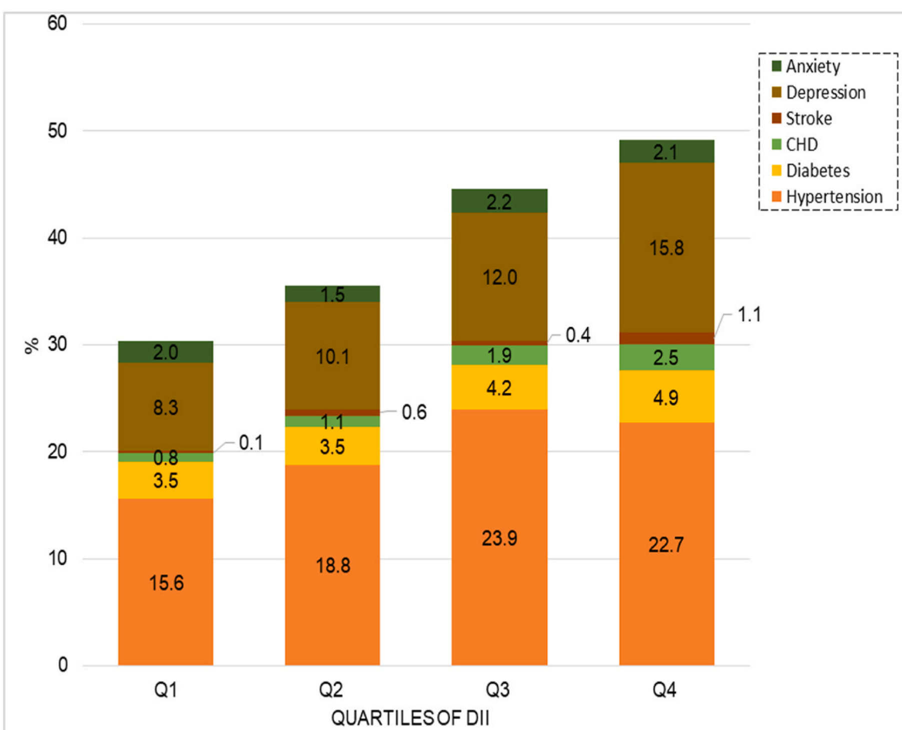

Fig. 2. Distribution of components of multimorbidity (CMDs and mental health disorders) across DII-quartiles (n = 5984)
APCAPS, the Andhra Pradesh Children and Parents Study; %, percent; DII, dietary inflammatory index; Q1, Q2, Q3, Q4 first, second, third, & fourth quartiles of DII.

after adjusting for the potential confounders (model 3). There was an evidence of dose-response relationship between DII and multimorbidity (model 3, p-trend 0.021). There was no evidence of interaction between DII and sex on multimorbidity (Figure-4). In an unadjusted model, a 1-SD (1.67 units) increase in DII was associated with a 52% higher multimorbidity [PR (95% CI) = 1.52(1.30, 1.77)]. This association (between DII and multimorbidity) was attenuated but remained significant with further adjustment for potential confounders [PR (95% CI) = 1.24(1.03,

Table-2
Distribution of socio-demographic and clinical parameters by the Multi-morbidity status.

Socio-demographic and clinical parameters		Overall (n = 5984)	Multimorbidity status: Absent (n = 5774)	Multimorbidity status: Present (n = 210)	p-value
Age in years, mean (SD)		36.2 (13.8)	35.9 (13.7)	45.4 (11.8)	<0.001
Male, n(%)		3179 (53.1)	3078 (53.3)	101 (48.1)	0.137
Standard of living score, mean (SD)		28.6 (8.5)	28.7 (8.5)	27.3 (7.7)	0.023
Education, n (%)	No formal education	2370 (39.6)	2241 (38.8)	129 (61.4)	<0.001
	Primary	1351 (22.6)	1299 (22.5)	52 (24.8)	
	Secondary	1784 (29.8)	1760 (30.5)	24 (11.4)	
	Beyond Secondary	479 (8.0)	474 (8.2)	5 (2.4)	
Occupation, n(%)	Unemployed	56 (0.8)	55 (0.8)	1 (0.4)	0.019
	Housewife/ retired/student	1550 (25.9)	1498 (25.9)	52 (24.8)	
	Unskilled laborer	2862 (41.3)	2756 (41.2)	106 (45.9)	
	Manual (Semi-skilled & Skilled)	1331 (22.3)	1287 (21.9)	44 (20.9)	
	Skilled non-manual/semi-professional and professional	344 (5.8)	330 (5.7)	14 (6.8)	
Physical activity level, mean (SD)		1.62 (0.21)	1.62 (0.21)	1.58 (0.21)	0.047
Moderate to Vigorously Physical active (yes), n(%)		1820 (30.4)	1766 (30.6)	54 (25.7)	0.007
BMI in kg/m^2, mean (SD)		20.9 (3.8)	20.9 (3.8)	22.5 (4.1)	<0.001
Current Smoker (yes), n(%)		1471 (24.6)	1390 (24.1)	81 (38.6)	<0.001
DII, median (IQR)		1.44 (0.07, 2.57)	1.41 (0.04, 2.56)	2.09 (1.00, 2.96)	<0.001

APCAPS, the Andhra Pradesh Children and Parents Study; BMI, body mass index; CMDs, cardio-metabolic diseases; DII, dietary inflammatory index; IQR, inter-quartile range; n, frequency; %, percent; Q1, Q2, Q3, Q4 quartiles of DII; SD, standard deviation.
CMDs included hypertension, diabetes, MI, heart failure, angina, and stroke; mental health disorders included depression and anxiety; 'Multimorbidity' was defined as a co-existence of one or more CMDs and one or more mental health disorders.
Participants were classified as current smokers if they reported current use of cigarettes or having stopped smoking within the past 6 months.

1.48)] (Figure-4).

In the propensity analysis, participants with multi-morbidity have had 0.48 units (95% CI: (0.06, 0.91) higher DII compared to participants without multi-morbidity. The results were nearly similar when we repeated the analyses using different definitions of Multimorbidity (SI-table 3).

4. Discussion

In the cross-sectional analyses of the APCAPS third follow-up data, we found that: (a) ~75% of the study participants had pro-inflammatory dietary pattern (DII >0.0); (b) 3.5% participants had co-existing one or more CMDs and one or more mental health conditions; (c) Dietary inflammation was strongly and positively associated with multi-morbidity of CMDs and common mental health disorders independent of potential confounders; (d) There was a trend for higher prevalence of multimorbidity with higher dietary inflammation. The hypothesis tested in this study was that the participants with higher DII score would have a higher burden of multimorbidity than those with lower DII score. Our results support this hypothesis. The graded and continuous relationship between dietary inflammation and multimorbidity suggests that even modest reduction in the levels of dietary inflammation may have an impact on reducing CMDs, mental health disorders and their clustering in the study population. To our knowledge, this is the first study from India which quantitatively assessed the inflammatory potential for the Indian diet and its association with CMDs, mental health disorders and their clustering in an urbanizing population.

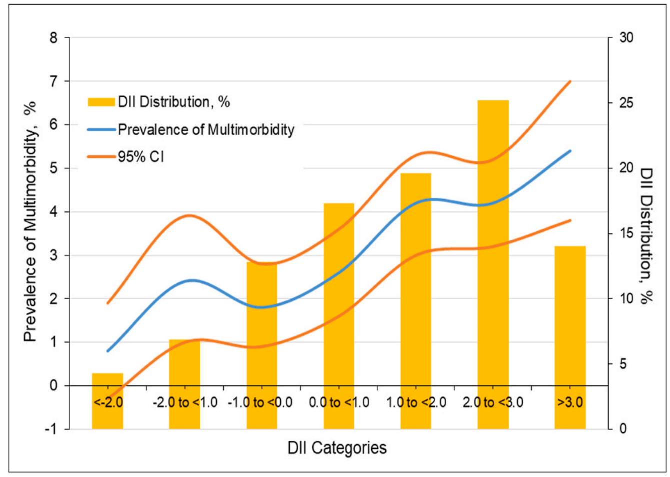

Fig. 3. Crude prevalence of Multimorbidity by DII categories (n = 5984) APCAPS, the Andhra Pradesh Children and Parents Study; %, percent; DII, dietary inflammatory index.

4.1. *Suboptimal consumption of fruits and green leafy vegetables (FGLV)*

In the study population, the higher DII among individuals appeared to be due to very less consumption of anti-inflammatory nutrients (minerals, vitamins and dietary fiber) rather than higher consumption of inflammatory nutrients (except total cholesterol). This could be largely explained by suboptimal consumption of *FGLV (*rich source of fibre, vitamins, minerals and antioxidants) (SI-table 1). In a qualitative study based on the APCAPS cohort, Turner et al. has reported that accessibility, availability and high price of fresh produce as the key barriers to increasing FGLV [24]. Author also mentioned that although participants were concerned about dietary related health issues, their nutrition literacy was limited and they were unaware of what constitutes a healthy diet as well as the consequences of unhealthy diet [24]. The APCAPS villages are experiencing rapid but uneven economic development since two decades which might be shifting the ways of life from agricultural to non-agricultural practices fuelling nutrition transition resulting into unhealthy diet (rich in inflammatory nutrients) [24]. Behavioral or lifestyle interventions (such as financial incentives) targeting to enrich diet with anti-inflammatory nutrients (increase consumption of FGLV) may reduce the burden of CMDs, mental health disorders and other nutrition-related disorders in this dynamic community.

4.2. *Comparison of findings with published literature*

Consistent with previous research, increasing age, being female, low SES, less physically active and higher BMI were positively and significantly associated with the multimorbidity [25]. Our findings extend the evidence by showing increased clustering of CMDs and mental health disorders in people from the transitional rural communities with pro-inflammatory dietary pattern. Our findings may provide a potential explanation (increased dietary inflammation) for the frequently observed co-occurrence of CMD-risk factors or events, and common mental health disorders [16,26,27]. This co-occurrence could be due to

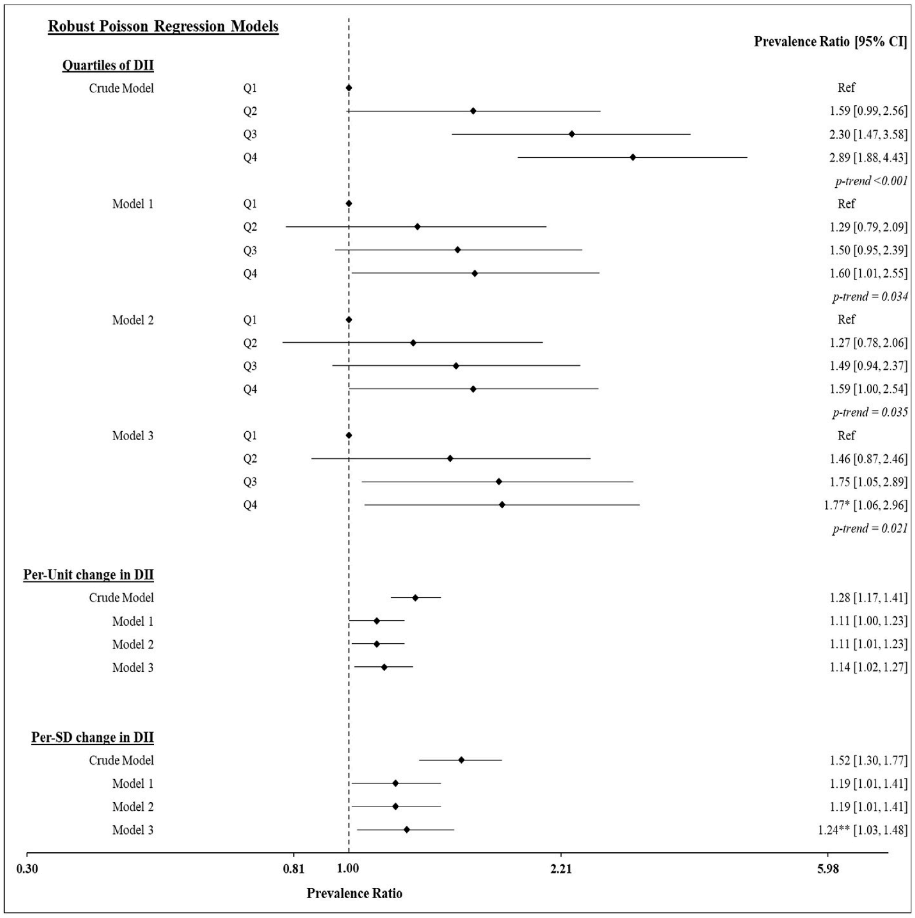

Fig. 4. Association between DII and Multimorbidity: Prevalence ratio (95% confidence interval) for Multimorbidity by DII-quartiles, per unit, and SD change in DII for the third follow-up of the APCAPS cohort (2010-12) (n = 5984)
APCAPS, the Andhra Pradesh Children and Parents Study; CI, confidence interval; DII, dietary inflammatory index; Ref, referent value; Q1, Q2, Q3, Q4, first, second, third, fourth DII-quartile. Robust Poisson Regression Models:
Crude model - DII Index; Model 1 - Crude model + age and sex; Model 2 - Model 1 + education and occupation; Model 3 - Model 2 + tobacco consumption, PAL, and BMI.
p-trend shows a p-value for linear trend across DII-quartiles;
*PR of 1.77 means that participants with fourth DII-quartile were 77% more likely to have the Multimorbidity compared to participants with the first DII-quartile after adjusting for
he effect of potential confounders on the multimorbidity.
**PR of 1.24 means that a 1-SD (1.67 units) increase in DII made a participant in this study 24% more likely to have the multimorbidity after adjusting for the effect of potential confounders on the Multimorbidity.

shared metabolic and inflammatory processes for example elevated insulin resistance and plasma homocysteine level, and more importantly increased production of pro-inflammatory cytokines and endothelial damage. A longitudinal [16] and cross-sectional study [26] have reported the detrimental effect of a pro-inflammatory diet on depression particularly among individuals diagnosed with CMDs. Similarly, in the PREDIMED trial [27], the authors have reported that adherence to a Mediterranean dietary pattern was particularly important to prevent depression among participants with CMDs. The possible explanation for the elevated risk of mental health problems among individuals with CMDs may be: maladaptive stress responses among individuals diagnosed with one of the physical conditions; elevated low grade chronic inflammation; and hyper-reactivity of hypothalamic pituitary adrenal axis (HPA axis non-habituation) [28]. Thus, modifying diet in the context of a behavioral or lifestyle intervention among individuals with one chronic conditions could reduce the onset and progression of other conditions resulting in reduced multimorbidity burden and healthcare cost for the individual and the households. Our results support the notion that higher intake of anti-inflammatory foods and reducing the consumption of pro-inflammatory foods would reduce the risk of CMDs, anxiety, and depression, and underpins its (anti-inflammatory diet) importance as an effective supplementary therapeutic tool for these patients [29,30].

4.3. Strengths

Our study has several strengths. First, the large sample size was sufficient for evaluating the effects of exposure on disease co-occurrence including accounting for multiple potential confounders of the relationship between the diet and multimorbidity; Second, we used DII, a novel algorithm validated against various inflammatory markers across different countries, to assess the inflammatory potential of overall diet rather than individual dietary components; Third, assessment of micro- and macro-nutrients was done using a validated FFQ coupled with locally collected recipes, specifically designed to capture typical food consumption in the study setting.

4.4. Limitations

The findings of this study, however, should be interpreted in the light of several limitations. First, the possibility of response bias in diet data collection and therefore the misclassification of DII cannot be completely eliminated. However, the FFQ we used was validated to capture the local dietary pattern and administered by a trained interviewer. If present, we expect any exposure misclassification would mostly have been 'non-differential', thereby underestimating the strength of association of DII with multimorbidity of CMDs and common mental health disorders. Second, the possibility of 'agreement bias' while assessing anxiety and depression using questionnaire, cannot be excluded. Participants may have hidden the information related to symptoms suggestive of anxiety and depression to maintain socially acceptable behaviour and avoid any social stigma. However, the interviewer were highly trained to conduct interviews and interviews were conducted maintaining the privacy of the participants. If any, the agreement bias would have had increased the type two error and reduced the strength of association. Third, we cannot establish the temporality (i.e. direction of causation) of the association between dietary inflammation and multimorbidity based on a cross-sectional analysis. It is possible that people diagnosed with CMDs had modified their diet (after discussion with their physician) and started consuming a diet rich in anti-inflammatory nutrients. Whereas, participants experiencing the symptoms of common mental health disorders may have changed their dietary habits to consume more pro-inflammatory diet. Future longitudinal studies are warranted to explore the role of dietary inflammation in the onset and progression as well as the underlying mechanisms for CMDs and mental health disorders and their clustering. Fourth, although we have controlled for a variety of sociodemographic and clinical characteristics, the possibility of residual confounding cannot be excluded. Fifth, as we have examined the research question in relatively young and healthy population living in rural and urbanizing villages of India, caution may be needed when generalizing these results to other populations. Sixth, although it is preferable to account for all 45 parameters to calculate DII [14], we only had information for 27 food parameters. The 17 out of 18 excluded food parameters were characterized as anti-inflammatory [14], which may have resulted into more pro-inflammatory DII scores. Other studies which examined the association of DII and mental and cardiovascular health had nearly similar exclusions of food-parameters considered as anti-inflammatory [29,30]. Seventh, lack of information on genetics predisposing factors for CMDs and depression/anxiety for the APCPAS cohort. Indians are more prone to have higher CMDs and depression/anxiety compared to their european counterparts. We could not assess and therefore, could not completely exclude the possibility of genetic predisposition for the co-occurrence of CMDs and mental health conditions in the APCAPS cohort.

4.5. Public health implications

Amidst globalization, many lower middle income countries (including India) are experiencing urbanization and dietary transition (from FGLV to calorie-rich and nutrient sparse fried food) which could increase the burden of overweight, obesity, and diet-related noncommunicable diseases. Policymakers in India are struggling to identify optimal strategies to manage this dietary transition. Evidence concerning dietary inflammation and clustering of chronic physical and mental health conditions in general population is limited. This study has identified a modifiable risk factor (dietary inflammatory potential) for multimorbidity in a population experiencing the convergence of traditional rural and novel urban risk factors. The finding of this study, if replicated in longitudinal studies would help formulating policies promoting the intake of diet rich in nutrients with anti-inflammatory potential. Improving the health of rural and urbanizing population, for instance through multimorbidity prevention will positively impact economic productivity in India. This will be particularly significant as CMDs as well as mental health disorders develop at earlier ages in south Asians (during their economic productive years) [12].

In conclusion, in this community-based study of 5984 participants residing in rural and urbanizing part of southern India, more than 75% of participants were habitually consuming a pro-inflammatory diet, which was associated with an increased prevalence of multimorbidity of CMDs and mental health disorders. Therefore, implementing interventions/policies that encourage and enable people to consume diet low in pro-inflammatory nutrients and rich in anti-inflammatory nutrients could reduce the onset as well as clustering of chronic physical and mental health disorders. Furthermore, the effectiveness of anti-inflammatory diet in the management of CMDs and mental health disorders and their clustering needs to be examined using randomized controlled clinical trials.

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Authors' declaration

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors have no acknowledgments to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hnm.2024.200254.

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